## **PCT**

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### INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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US

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#### Published

With international search report.

(88) Date of publication of the international search report: 20 April 2000 (20.04.00)

(54) Title: APOPTOSIS MODULATORS THAT INTERACT WITH THE HUNTINGTON'S DISEASE GENE

#### (57) Abstract

A family of proteins, including a specific human protein designated as HIP1, has been identified that interact differently with the gene product of a normal (16 CAG repeat) and an expanded (>44 CAG repeat) HD gene. Expression of the HIP1 protein was found to be enriched in the brain. Analysis of the sequence of the HIP1 protein indicated that it includes a death effector domain (DED), suggesting an apoptotic function. Thus, it appears that a normal function of Huntingtin may be to bind HIP1 and related apoptosis modulators, reducing its effectiveness in stimulating cell death. Since expanded huntingtin performs this function less well, there is an increase in HIP1-modulated cell death in individuals with an expanded repeat in the HD gene. This understanding of the likely role of huntingtin and HIP1 or related proteins (collectively "HIP-apoptosis modulating proteins") in the pathology of Huntington's disease offers several possibilities for therapy. First, because the function of huntingtin apparently depends at least in part on the ability to interact with HIP-apoptosis modulating proteins, added expression (e.g., via gene therapy) of normal (non-expanded) huntingtin or of the HIP-binding region of huntingtin should provide a therapeutic benefit. Other DED-interacting peptides could also be used to mask and reduce the interaction of HIP-apoptosis modulating proteins with the death signaling complex. Alternatively, a mutant form of HIP-protein from which the DED has been deleted might be introduced, for example using gene therapy techniques. Because HIP-apoptosis modulating proteins have been shown to self-associate, a protein with a deleted DED may compete with endogenous HIP-protein in the formation of these associations, thereby reducing the amount of apoptotically-active HIP-protein.

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## INTERNATIONAL SEARCH REPORT

International application No. PCT/US99/11743

A. CLASSIFICATION OF SUBJECT MATTER  IPC(6) :C07H 21/04; C12Q 1/68; C07K 5/00  US CL :536/23.5; 435/6; 530/350									
\$	According to International Patent Classification (IPC) or to both national classification and IPC								
B. FIELDS SEARCHED									
Minimum documentation searched (classification system followed by classification symbols)									
U.S. :	536/23.5; 435/6; 530/350								
Documenta	tion searched other than minimum documentation to the	e extent that such documents are included	in the fields searched						
	data base consulted during the international search (na CAPLUS, MEDLINE	ame of data base and, where practicable	, search terms used)						
C. DOC	UMENTS CONSIDERED TO BE ALLEVANT								
Category*	Citation of document, with indication, where ap	propriate, of the relevant passages	Relevant to claim No.						
X	WANKER et al., HIP-I: A Huntingtin the Yeast Two-hybrid System. Human 1997, Vol. 6, No. 3, pages 487-495,	n Molecular Genetics. March	1-15						
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T Pro-at	ner documents are listed in the continuation of Box C	See patent family annex.							
		*T* leter document published after the inte	erational films date as a similar						
*A* do	ecial categories of cited documents:  cument defining the general state of the art which is not considered  be of particular relevance	date and not in conflict with the appl the principle or theory underlying the	ication but cited to understand						
	rijer document published on or after the international filing date	"X"  document of particular relevance; the considered novel or cannot be conside when the document is taken alone							
cit spe	cited to establish the publication date of another citation or other special reason (as specified)  *Y*  document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is								
*P* do	document referring to an oral disclosure, use, exhibition or other means  document published prior to the international filing date but later than  document member of the same patent family								
	priority date claimed actual completion of the international search	Date of mailing of the international sea							
	MBER 1999	3 February 2000 (03.02.0	•						
Commissio Box PCT Washington	nailing address of the ISA/US ner of Patents and Trademarks n, D.C. 20231	Authorized officer January Co. SCOTT HOUTTEMAN	2 /2						
Haccimile N	esimile No. (703) 305-3230 Telephone No. (703) 308-0196								

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#### From the INTERNATIONAL BUREAU

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#### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Date of mailing (day/month/year)

KALCHMAN, Michael et al

Assistant Commissioner for Patents United States Patent and Trademark Office **Box PCT** 

Washington, D.C.20231 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

08 March 2000 (08.03.00) International application No. Applicant's or agent's file reference PCT/US99/11743 UBC.P-013WO2 International filing date (day/month/year) Priority date (day/month/year) 27 May 1999 (27.05.99) 27 May 1998 (27.05.98) Applicant

To:

The designated Office is hereby notified of its election made: X in the demand filed with the International Preliminary Examining Authority on: 13 December 1999 (13.12.99) in a notice effecting later election filed with the International Bureau on: 2. The election was was not made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

> The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35



# PATENT COOPERATION TO ATY REC'D 25 SEP 2000



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## (PCT Article 36 and Rule 70)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Applicant's or agent's file reference MC010-PCT	FOR FURTHER ACTION		cation of Transmittal of International Examination Report (Form PCT/IPEA/416)					
International application No.	International filing date (day/n	onth/year)	Priority date (day/month/year)					
PCT/US99/11743	27 MAY 1999		27 MAY 1998					
International Patent Classification (IPC) or national classification and IPC IPC(7): CO7H 21/04; C12Q 1/68; C07K 5/00 and US Cl.: 536/23.5; 435/6; 530/350								
Applicant MERCK FROSST CANADA AND CO	J* UNIVERSIT	J & J	Risish (olutizia.					
Examining Authority and is  2. This REPORT consists of a to the second the se	transmitted to the applicant a total of sheets.  panied by ANNEXES, i.e., sheets basis for this report and/or she ion 607 of the Administrative tal of sheets.	ets of the desc eets containin Instructions u	ription, claims and/or drawings which have g rectifications made before this Authority.					
3. This report contains indication	s relating to the following it	ems:	9					
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II Priority			,					
III Non-establishmen	t of report with regard to no	veltv. invent	ive step or industrial applicability					
IV Lack of unity of i		· · · <b>,</b> ·						
V X Reasoned statemen			v, inventive step or industrial applicability;					
VI Certain documents			*					
	ne international application							
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VIII Certain observations	s on the international applicati	on						
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Date of submission of the demand	Data	of completion	of this report					
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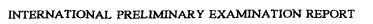
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international application No.

PCT/US99/11743

I.	Ba	sis O	f the repo	ort				
1. \	With	regard	d to the elem	ments of the internal	tional application:*	•		
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4.[	x	The	amendmei	nts have resulted	in the cancellat	ion of:		
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		$\overline{\mathbf{x}}$			7-8, 10-11			
		H		ns, Nos.				
_		X	the draw	ings, sheets <del>/fig</del> _	NONE			
5.	X ]		-	·	•			ney have been considered to go
							x (Rule 70.2(c)).**	d A
i	n thi	icements rep 70.17	ort as "ori	uch have been furni ginally filed" and	shed to the receive are not annexed	ing Office in re to this report	sponse to an invitation since they do not co	n under Article 14 are referred to Intain amendments (Rules 70.16
				et containing such	amendments mu	st be referred	to under item 1 and	annexed to this report.



International application No.

PCT/US99/11743

statement					
Novelty (N)	Claims	1-6, 9, 12-15			Y
•	Claims				N
Inventive Step (IS)	Claims	1-6, 9, 12-15			Y
, ,	Claims				_
Industrial Applicability (IA)	Claims	1-6, 9, 12-15			
nicusulai Appheaomity (M)	Claims	NONE			
protein encoded by SEQ ID NOS. 2, 4 5 or screening for apoptosis inhibiting activity.		ous of use of HD interact	ung process in r	educing apopt	osis or
NONE					



#### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

international application No.

PCT/US99/11743

#### Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

#### I. BASIS OF REPORT:

This report has been drawn on the basis of the description, page(s) 1-31, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims, page(s) NONE, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Pages 32-33, filed with the letter of 15 August 2000.

This report has been drawn on the basis of the drawings, page(s) 1-12, as originally filed. page(s) NONE, filed with the demand. and additional amendments:

NONE

This report has been drawn on the basis of the sequence listing part of the description: page(s) 1-44, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

5. (Some) amendments are considered to go beyond the disclosure as filed:  $\ensuremath{\mathsf{NONE}}$ 

## **CLAIMS**

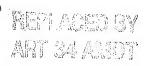
1	1.	A polypeptide comprising the sequence given by Seq. 1D. No. 3.
1	2.	A cDNA molecule comprising the sequence given by Seq. ID No. 6.
1	3.	A polypeptide comprising the sequence given by Seq. ID No. 7.
1	4.	A method for ameliorating the effects of Huntington's disease in a
2	patient expressing a	HIP-apoptosis modulating protein, comprising the step of administering
3		atic composition which reduces the activity of the HIP-apoptosis
4	modulating protein.	
1	5.	A method according to claim 4, wherein the composition comprises a
2	material which binds	to HIP-apoptosis modulating protein.
1	6.	The method according to claim 4, wherein the composition comprises
2	an expression vector	encoding huntingtin having a normal number of repeats.
1	7.	An expression vector for expression of a gene in a mammalian host
2	comprising a region	encoding an HD-interacting polypeptide.
1	8.	The expression vector according to claim 7, wherein the HD-
2	interacting polypept	de is an HIP-apoptosis modulating protein.
1	9.	The expression vector according to claim 8, wherein the HIP-apoptosis
2	modulating protein l	nas a sequence which includes the amino acid sequences given by SEQ
3	ID Nos. 2, 4, 5 or 7.	



4

and measuring the extent of cell death.

1	10. The expression vector of claim 7, wherein the HD-interacting							
2	polypeptide interacts differently with expanded Huntingtin than with Huntingtin having a							
3	CAG repeat region containing 15 to 35 repeats.							
1	11. The expression vector according to claims of claims 7-10, further							
2	comprising a region encoding Huntingtin having a polyglutamine tract of 35 or fewer.							
1	12. A method for inducing apoptotic death in cells, comprising the step of							
2	introducing into the cells an expression vector encoding at least the death effector domain of							
3	a HIP-apoptosis modulating protein whereby the death effector domain is expressed by the							
4	cells.							
1	13. The method of claim 12, wherein the expression vector encodes the							
2	amino acid sequence given by Seq. ID. No. 2.							
1	14. The method of claim 12, wherein the expression vector encodes the							
2	amino acid sequence given by Seq. ID. No. 4.							
1	15. A method for screening a composition for the ability to inhibit							
2	apoptosis induced by an HIP-apoptosis modulating protein, comprising simultaneously							
3	exposing a population of cells to the composition and an HIP-apoptosis modulating protein							





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## NOTE ON INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No. PCT/US99/11743		Applicant's or agent's i	üle reference	(day/month/year)	Date of informal communication (day/month/year) 15 AUGUST 2000			
Applicant MERCK FROSST CANADA AND CO.,								
Communication  X by telephone  personal	Participants  Applicant  X Agent:  X Examiner	Mr. Joseph A. (		authorization checked	personally known			
Summary of communication:  The examiner and the applicant's rep. agreed to claim amendments.								
*								
-								
An extension of time limit is granted (Form PCT/IPEA/427).								
X A copy of this note is	being sent to	the applicant with For	m <del>РСТ/ІРЕА/42</del> 9 РСТ/ІРЕА/		,			
Applicant/Agent  Mr. Joseph A. Coppola			Authorized offi SCOTT HOU Telephone No.	JI I DIMIN	nce fa			